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BULLETIN

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CONTENTS

Experimental and Human Atherosclerosis: Possible Relationship and Present Status 539
Maurice Bruger and Elliot Oppenheim

ACTH and Cortisone as Therapeutic Agents in Arthritis and Some Locomotor Disorders 560
Otto Steinbrocker, Sidney Berkowitz, Solomon Carp, Mortimer Ehrlich, Mortimer Elkind, Murray Silver and Norman Spitzer

Recommendations for Action to Relieve the Nursing Shortage 577

Section on Microbiology:

Studies on the Mechanism of the Toxic Action of Newcastle Disease Virus, *Harold S. Ginsberg* 581

Studies on the Relationship between the Theiler Group of Viruses and the Intestinal Tract of the Mouse, *Benjamin Mandel* 583

Chromatographic Analysis of Ragweed Pollen Extract, *Ely Perlman* 586

Library Notes:

Recent Accessions to the Library 590

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BULLETIN OF
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EXPERIMENTAL AND HUMAN ATHEROSCLEROSIS: POSSIBLE RELATIONSHIP AND PRESENT STATUS*

MAURICE BRUGER AND ELLIOT OPPENHEIM

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In this review, we are concerned with only one form of arteriosclerosis, namely, that associated with deposition of lipids in the intima. This form of arteriosclerosis was first named atherosclerosis by Marchand[1] and is a disorder which involves the aorta and its visceral branches as well as the coronary and cerebral arteries.

While the lesions of arteriosclerosis have been recognized for over 400 years, the changes in the arteries were regarded by the earlier anatomists as the natural result of ageing and therefore not an abnormal process. This concept of the inevitability of the disease is untenable. One fact is abundantly clear—atherosclerosis is not the exclusive stigma of age. French and Dock[2] reported the high incidence of coronary artery disease in men under thirty-five years of age in the American Army. Eight cases have been reported of atherosclerosis with sudden death in children sixteen years of age or younger.[3] Today, atherosclerosis

* This paper is an extension of a lecture entitled "Experimental Cholesterol Atherosclerosis and Its Possible Relationship to the Human Problem" given by the senior author in the Friday Afternoon Lecture Series at The New York Academy of Medicine on January 27, 1950.

TABLE I—REASONS FOR IMPLICATING CHOLESTEROL AS AN IMPORTANT ETIOLOGIC AGENT IN THE PATHOGENESIS OF ATHEROSCLEROSIS

1.	Cholesterol is constantly present in atherosclerotic plaques.
2.	The oral or parenteral administration of cholesterol to susceptible animals will result in the production of atherosclerotic lesions in the elastic arteries.
3.	With the exception of macromolecular substances, e.g., polyvinyl alcohol, methyl cellulose, pectin and acacia, no agent other than cholesterol will produce the typical atherosclerotic lesion.
4.	Intimal lipid deposition and atherosclerosis are rare in wild animals, which seldom, if ever, eat a meal containing the amount of fat found in the average human diet.
5.	Human atherosclerosis is prominent in those clinical states accompanied by hypercholesterolemia, e.g., diabetes mellitus, myxedema, nephrosis, familial hyperlipemia, primary xanthomatosis, etc.
6.	Atherosclerosis is rare in peoples consuming low or nearly fat-free diets.
7.	Atherosclerosis decreased notably in war-torn areas during the fat-shortage years immediately following World War I.
8.	Atherosclerosis is more common in obese, overnourished persons than in the lean and undernourished.
9.	This lesion is less severe and less common in chronic alcoholics who presumably eat less, especially less fat, for which they have an intolerance.

is recognized as the most widespread and significant lesion involving the vascular system. The effect of its presence in the coronary and cerebral arteries in the young and in the old constitutes a major clinical problem.

Virchow[4] was the first to call attention to the fact that the changes which occurred in the intima were initiated by the invasion of the blood plasma. Aschoff,[5] Windaus[6] and Schönheimer[7] established the fact that the deposited lipid consisted mainly of cholesterol esters. Thus, the metabolic concept was initiated which implicated cholesterol as a possible cause of atherosclerosis.

The pathogenesis of human atherosclerosis probably depends on three factors, namely: (a) abnormal cholesterol metabolism, (b) constitutional or hereditary disposition and (c) physical and chemical changes in the elastic wall of the artery as influenced by blood pressure, ageing, etc. It cannot be stated which of these factors are primary and which are secondary. Recent investigations have emphasized the role of cholesterol in the hope that the metabolism of this sterol may be controlled by drugs and/or dietary means. Table I presents some of the clinical and experimental observations that have been offered to substantiate the concept that this sterol plays an important part in the etiology of atherosclerosis.

TABLE II—EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS

Susceptible Animals	*Non-Susceptible Animals*
1. Rabbit	1. Rat
2. Guinea pig	2. Mouse
3. Dog (with simultaneous thiouracil feeding)	3. Cat
4. Chick	4. Goat
5. Goose (forced feeding)	5. Fox
6. Golden hamster	6. Pigeon
7. Prairie gopher	7. Parrot
	8. Monkey

EXPERIMENTAL ATHEROSCLEROSIS

Since atherosclerosis was first produced in rabbits by the feeding of cholesterol,[8] many attempts have been made to produce the lesion in other animals by the ingestion of cholesterol. Table II indicates those animals which are or are not prone to experimental cholesterol atherosclerosis. The rabbit is by far the most susceptible laboratory animal and much of the experimental work in this field has been done with it. The effects of various agents on the development of atherosclerosis in the rabbit during cholesterol feeding are shown in Table III. These agents may accentuate or inhibit the deposition of this sterol in the intima; some have no effect and are classified as neutral agents.

Inhibitory Agents

1. *Iodides:* Murata and Kataoka[9] noted that the feeding of iodine prevented the deposition of cholesterol in the arterial wall of rabbits fed cholesterol. This was later confirmed by other workers.[10-14] Turner and Khayat[15] showed that thyroidectomy abolished this protective action of potassium iodide; this was not confirmed by Brown and Page.[16] In dogs, potassium iodide had no effect on the absorption of cholesterol from the gastrointestinal tract.[17]

2. *Thyroid:* Turner[12] showed that the feeding of desiccated thyroid to cholesterol-fed rabbits inhibited the deposition of cholesterol in the vessels of these animals. A possible relationship between experimental atherosclerosis and the function of the thyroid gland was thus established.

3. *Thiocyanates:* In thyroidectomized rabbits, potassium thiocyanate exercised a protective action against the development of cholesterol

TABLE III—EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN THE RABBIT

Inhibitory Agents	*Neutral Agents*	*Accentuating Agents*
Iodides	Vitamin A	Vitamin E (massive doses)
Thyroid	Thiamine chloride	Glycocholic acid
Thiocyanate	Ascorbic acid	Cholic acid
Alcohol	Vitamin E	Olive oil
Estrogenic hormones in females	Desoxycorticosterone acetate	Uranium
Androgenic hormones in females	Estrogenic hormones in males	Thyrotropic factor of anterior pituitary
Alloxan diabetes	Androgenic hormones in males	Lithium iodide } given
Detergents (intravenous administration of Aerosol OT, Triton NE and Tween 80)	Dehydrocholic acid	Potassium cyanide } together
Lipotropic agents (?)	Hyodesoxycholic acid	Detergents (oral administration of Triton NE and Tween 80)
Choline	Desoxycholic acid	
Lipocaic	Liver extract	
Soya lecithin	Chloroform vapor	
Betaine		
Methionine		
Inositol		
Benzol		

atherosclerosis.[18] This was confirmed by Hueper[19] in rabbits with intact thyroid glands. He felt that the preventive action of this agent was not due to a lowering of the blood cholesterol or to an increase in the production of thyroid hormone but rather to the stabilizing effect of thiocyanate on the colloidal equilibrium of the plasma.

4. *Alcohol:* Eberhard[20] studied the effect of alcohol on cholesterol-induced atherosclerosis in rabbits. He found that the cholesterol content of the blood rose more rapidly and to a higher level in the animals receiving both substances than in those receiving cholesterol alone. The deposition of cholesterol in the liver and aorta, however, occurred in an inverse ratio. These findings were not confirmed by Thiersch.[21]

5. *Sex Hormones:* No noteworthy changes were found in the cholesterol content of the blood or the aorta in male or female rabbits receiving 450 mg of testosterone propionate and 9 mg of estradiol dipropionate, respectively, in divided doses over a period of one hundred days.[22] In female rabbits fed cholesterol, the development of hypercholesterolemia was inhibited and the deposition of cholesterol in the

aorta was prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol, these steroids exerted little or no protective action.[23] To determine whether the female gonads were necessary for the exhibition of this protective property by the steroid hormones, the above experiment was repeated using castrate female rabbits. The protective action was abolished by castration.[24]

6. *Alloxan Diabetes:* In 1943, it was shown that rabbits could be made permanently diabetic with alloxan.[25] Such animals exhibited gross lipemia but atherosclerotic lesions were not observed in short-term experiments.[26] On closer examination, it was found that the lipemia in alloxan-diabetic rabbits was transient and inconstant, while the blood cholesterol was frequently elevated to about 350 mg per cent. The blood cholesterol almost always returned to normal in three to six weeks and remained so during the remainder of the life of the animal in spite of the persistence of severe diabetes.[27-29] Atherosclerosis did not develop in periods up to one year.

Duff and McMillan[28] fed cholesterol to rabbits already made diabetic with alloxan. Insulin was used to control the diabetes in the early periods after alloxan but was not used during cholesterol feeding. Cholesterol administration was begun only after the diabetes was well stabilized. Low intakes of cholesterol produced neither hypercholesterolemia or atherosclerosis in either control or diabetic rabbits. With higher doses, the control rabbits consistently showed hypercholesterolemia and severe atherosclerosis. The diabetic rabbits receiving equivalent amounts of cholesterol showed a striking resistance to the development of atheromatous lesions though their blood cholesterol, both free and esterified, was increased to the same degree as in the control animals.

At first glance it is difficult to reconcile these findings with the higher incidence of atherosclerosis in human diabetics. Firstbrook[30] recently demonstrated the importance of body weight on the production of atherosclerosis in rabbits. If the food intake of the animals fed cholesterol was diminished, the incidence of atherosclerosis was also decreased. As pointed out by Adams,[31] this work makes it appear that the low incidence of experimental atherosclerosis in rabbits rendered diabetic with alloxan before cholesterol feeding is probably associated with the characteristic emaciation of these animals rather than to a specific effect of the diabetes.

7. *Detergents:* Hueper[32] investigated the effect of various detergents on experimental cholesterol atherosclerosis in rabbits. An increase in serum cholesterol occurred early in the experiments due to an elevation of free cholesterol. In 2 rabbits given Aerosol OT intravenously, the arterial changes were restricted to medial degeneration and calcification of the aorta in 1 rabbit, while in the group given Aerosol orally such lesions appeared in association with mild to moderate atheromatous reactions in the ascending portion of the aorta. Using Triton NE orally, Hueper found a rapid and persistent elevation of serum cholesterol associated with marked and diffuse atheromatosis.

Kellner et al[33, 34] found that when Tween 80 was added to the diet of cholesterol-fed rabbits, cholesterol absorption was increased as revealed by elevated cholesterol levels in the blood and accelerated atherosclerosis. When the detergent was given intravenously, atherosclerosis was retarded in spite of a hyperlipemic creamy plasma. These workers believed that the associated elevation in phospholipids which occurred simultaneously stabilized the plasma cholesterol and thus prevented its deposition in the elastic arteries. Payne and Duff[35] reported recently that the inhibition of the atherosclerosis cannot with certainty be attributed to the elevated phospholipids. They showed that the injected detergent remained in the blood stream for long periods of time so that it might have an inhibitory effect independent of the serum lipid changes.

8. *Lipotropic Agents:* The effect of various lipotropic substances on experimental atherosclerosis has received much attention. Steiner[36] maintained that choline fed with cholesterol appeared to delay but did not prevent the appearance of atherosclerosis in rabbits. Choline given alone reputedly produced a resolution of aortic lesions previously induced by cholesterol feeding. This was confirmed by other workers.[37, 38] On the other hand, Baumann and Rusch,[39] Himsworth[40] and Firstbrook[41] were unable to prevent the formation of aortic atheroma by choline feeding.

Huber et al[42] found that lipocaic did not affect the level of blood cholesterol in normal rabbits but this agent prevented a rise in blood cholesterol and the development of atherosclerosis in the aorta in rabbits fed a diet high in cholesterol. This work was not confirmed by Dragstedt and his co-workers.[43]

The partial protection apparently afforded by soy bean flour against

cholesterol-induced atherosclerosis in rabbits[44] led Kesten and Silbowitz[45] to investigate the effect of soya lecithin. They found that it restricted hypercholesterolemia and diminished the incidence of atherosclerosis.

Methionine, betaine and inositol have been reported without significant effect in experimental cholesterol atherosclerosis.[38]

9. *Benzol:* Altschul,[46] in a small series, found that benzol inhibited the deposition of cholesterol in the aorta of rabbits.

Neutral Agents

Certain substances have been found to have neither an accentuating or inhibiting effect on experimental cholesterol atherosclerosis. These include vitamin A,[47] thiamin chloride,[48] ascorbic acid,[48] vitamin E,[49] desoxycorticosterone acetate,[50] estrogenic and androgenic hormones in males,[23] various bile acids such as dehydrocholic acid, hyodesoxycholic acid and desoxycholic acid,[51] liver extract,[52] and chloroform vapor.[53]

Accentuating Agents

1. *Vitamin E:* Dam[49] reported that vitamin E given orally to cholesterol-fed rabbits did not augment the deposition of cholesterol deposited in the aorta. One of us,[54] on the other hand, found that the administration of 100 mg of vitamin E injected three times weekly for twelve weeks augmented appreciably the deposition of cholesterol in the aorta. The apparent discrepancy between these two studies may be ascribed to the different routes and dosages employed by the two investigators.

2. *Glycocholic and Cholic Acid:* Schönheimer[55] showed that desoxycholic acid hastens the absorption of cholesterol from the intestinal tract of mice and rabbits. Hummel[56] and Loeffler[57] reported that the simultaneous feeding of bile salts and cholesterol to mice caused a considerable deposition of this sterol in the liver.

The present authors in collaboration with Member[51] studied the effect of a selected bile acid when fed with cholesterol on the amount of this sterol deposited in the aorta of the rabbit. They found cholic or glycocholic acid fed with cholesterol increased markedly the cholesterol content of whole blood and aorta as compared with values obtained following the ingestion of cholesterol alone. Dehydrocholic acid, hyodesoxycholic acid and desoxycholic acid did not possess this property.

3. *Olive Oil:* In studies on rats, guinea pigs and rabbits, Cook and McCullagh[58] showed that the feeding of cholesterol in oil increased the blood cholesterol and hepatic lipids of the rat; in the guinea pig, the blood cholesterol alone was augmented; in the rabbit, the blood, the liver and the aorta showed high concentrations of cholesterol. Member and Bruger[59] studied the effect of the feeding of olive oil on the absorption and deposition of cholesterol in the rabbit. They found that olive oil fed with cholesterol produced only slightly higher blood cholesterol levels than did the feeding of cholesterol alone; an appreciable increase in the deposition of cholesterol in the liver and aorta, however, was noted.

4. *Uranium:* Rabbits with dietary hypercholesterolemia of short duration developed aortic atherosclerosis abruptly after the production of renal damage by the administration of uranium acetate.[60]

5. *Thyrotropic Factor of Anterior Pituitary:* The intraperitoneal administration of the thyroid stimulating hormone of the anterior lobe of the pituitary gland over a protracted period of time to rabbits fed cholesterol was accompanied in most instances by an increase in the deposition of cholesterol in the aorta compared to control animals receiving cholesterol alone.[61]

Probable Factors and Pathways in the Pathogenesis of Atherosclerosis

Despite the wide disagreement on many aspects of atherosclerosis, one fact remains clear – the predominant lipid in the atherosclerotic plaque is cholesterol. Why this is so or how this sterol is deposited is a matter of much debate. At the outset, one must acknowledge that there is no single cause of atherosclerosis. The pleomorphism of the process, its characteristic irregularity of distribution and rate of development are evidence that this is so. Several factors are at work and the end result may be arrived at in different ways. Figure 1 is an attempt to correlate those factors which predispose to the development of atherosclerosis (atherogenic) and those which oppose it (anti-atherogenic).

To begin with one must consider the nutrition of the vessel wall. Ramsey[62] states "three possible mechanisms must be recognized; namely, nutrition through vasa vasorum; nutrition from the lumen of the vessel; or nutrition by way of the canal system communicating, directly or

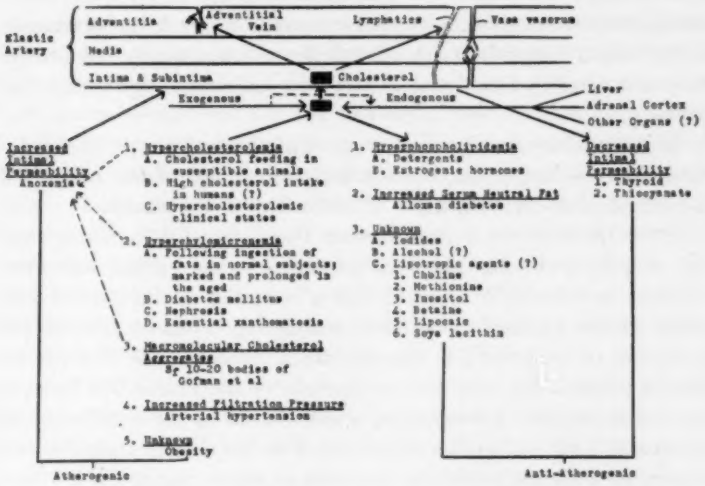

Fig. 1. Probable Factors and Pathways in the Pathogenesis of Atherosclerosis

indirectly, with the vasa vasorum or the lumen. Now, as in 1875, it is impossible to state which of these mechanisms, or what combinations of them, are operative, or what role is played by lymphatics." An acceptable concept of the nutrition of the vessel wall is as follows: the adventitia and outer portion of the media are supplied by the vasa vasorum from the outer surface of the vessel. The intima and adjacent portion of the media are nourished by the blood flowing within the lumen of the vessel. In addition, there is probably direct diffusion of blood across the intact endothelial membrane of the intima. Normally, a constant stream containing water, salt, sugar and lipids flows through the walls of the large arteries and thence to the lymphatics and veins of the adventitia.[63-66] Factors which interfere with the nutrition of the vessel wall conceivably may participate in the development of atherosclerosis. Winternitz[67] believes that minute hemorrhages and thrombi in the vessel wall with subsequent sclerosis is a primary cause of arteriosclerosis. He considers the presence of cholesterol in the lesion to be a secondary manifestation. Hirsch and Weinhouse[68] maintain that cholesterol is deposited only after some primary arterial damage has occurred.

Most workers, however, agree that cholesterol deposition is the initial pathogenic process. Several theories exist as to its mode of localization in the intima. Anitschkow felt that cholesterol was simply imbibed by the intima when its concentration reached a sufficiently high level in the plasma.

It is probable that the deposition of cholesterol in the intima depends on two factors: namely (a) the permeability of the intima and (b) the physico-chemical status of cholesterol in the plasma.

Permeability of the Arterial Intima: The endothelial membrane consists of a layer of cells and some connective tissue ground substance. Virchow and Aschoff[69] believed that a loosening of this ground substance caused by mechanical strain and ageing occurred prior to the deposition of cholesterol in the sub-intima. Hueper[70] felt that the increased permeability was due to anoxemia of the intima. He believed that under certain circumstances, a disturbance in the equilibrium of the plasma lipids occurred which affected the stability of their colloidal dispersion. This resulted in the formation of coarse aggregates and their precipitation on the arterial intima. Owing to the chemically inert nature of cholesterol, Hueper felt that such intimal films impaired the normal exchange of gases and nutritive substances across the interface between the blood stream and the intima and thus gave rise to an increased permeability of the injured endothelial lining and to the deposition of lipid material in the intima. He showed that repeated intravenous or intraperitoneal injections of various highly polymerized macromolecular carbohydrates such as polyvinyl alcohol, methyl cellulose, pectin or acacia elicited atheromatous reactions which were morphologically identical with those seen in man and with those produced in rabbits by the feeding of cholesterol. Since these substances were as inert chemically as was cholesterol, he postulated that these macromolecular carbohydrates form a thin film overlying the intima interfering with its nutrition with resultant increased permeability of the membrane.

Physico-Chemical Status of Cholesterol

1. *Hypercholesterolemia:* The relationship between experimental hypercholesterolemia and atherosclerosis in the rabbit has been discussed above. Although it is agreed that the lipid metabolism of the rabbit differs in certain aspects from that of man, it is clear that in both

species there appears to be a correlation between the level of the plasma cholesterol and the development of the atherosclerotic plaque. In the human, such clinical disorders as essential xanthomatosis, familial hyperlipemia, diabetes mellitus, hypothyroidism and nephrosis are associated with hypercholesterolemia and an increased incidence of atherosclerosis.

Whether patients with atherosclerosis as a group have higher blood cholesterol levels than those without this lesion is a subject of much debate. Lande and Sperry[71] obtained aortic blood from individuals shortly after death and found no consistent correlation between the level of the blood cholesterol and the presence of atherosclerosis. On the other hand, several studies have shown that while some noteworthy exceptions occur, atherosclerotic individuals as a group manifest higher blood cholesterols than those without sclerosis.[72-76]

2. *Hyperchylomicronemia:* In 1924, Gage and Fish[77] demonstrated that the plasma of normal humans in the fasting state contains very few lipid particles of sufficient size to be visible by dark-field microscopy. After a fatty meal, however, large visible particles (chylomicrons) appear in great numbers. These observations were extended and correlated with blood lipid studies by Frazer and Stewart.[78] Moreton[79] noted that the chylomicrons which appeared in large numbers three to five hours after the ingestion of fat were identical with the lipid particles which were observed in clinical conditions of sustained hyperlipemia such as diabetes mellitus, nephrosis and essential xanthomatosis. The alterations in the physical state consisted of greater numbers of lipid particles of considerably larger size than those found in normal fasting plasma or after fat-free meals. Moreton assumed that the cumulative effect of many fatty meals over a lifetime (by producing transient showers of large lipid particles in the plasma) might be the underlying cause of the intimal lipid deposition in humans. Recently, utilizing a fat tolerance test in the form of heavy cream, Moreton[80] found considerable differences in the fat tolerances of normal subjects. Repeated tests at intervals of 6 months showed that an individual pattern of fat tolerance remained rather constant. The degree of chylomicronemia, following a fatty meal, was affected by age, sex, obesity, familial patterns, pancreatic function and other factors. Subsequently, Becker, Meyer and Necheles[81] reported that a fat test meal produced a considerably greater and more prolonged increase in the chylomicron count in elderly subjects compared to young persons.

3. *Macromolecular Cholesterol Aggregates:* Recent studies by Gofman and his co-workers[82-84] suggested an association between a particular type of cholesterol-bearing molecule and the development of atherosclerosis. They used the analytical ultracentrifuge in which different rates of flotation (negative sedimentation) of cholesterol-containing protein molecules were determined. According to the scale of the flotation rates reported, serum normally contained lipoproteins of S_f 5 to 8 size. In rabbits fed 3 grams of cholesterol per week for fifteen weeks, an increase in the S_f 5 to 8 components was noted. In some rabbits, however, new molecular components of a S_f 10 to 30 class appeared after thirty to forty days of cholesterol feeding. At necropsy, a definite correlation was observed between the extent of atherosclerosis and the appearance of the S_f 10 to 30 components.

In their study on human sera, the normal S_f 3 to 8 components were constantly found. In some cases, however, the presence of molecular species of S_f 10 to 20 was noted. After investigating many sera of subjects in different age groups and of patients with myocardial infarction or diabetes mellitus, Gofman and his co-workers concluded that the S_f 10 to 20 class of components was specifically related to the development of atherosclerosis. They stated that although there was a trend for sera with increased concentrations of cholesterol to contain S_f 10 to 20 molecules, the correlation was not satisfactory. Many blood specimens with a total cholesterol content over 200 mg per cent showed the presence of S_f 10 to 20 molecules but many did not. Likewise, many sera with normal total cholesterol values contained S_f 10 to 20 molecules. In bloods containing over 300 mg per cent of total cholesterol, S_f 10 to 20 molecular fractions were generally increased.

4. *Role of Phospholipids:* The importance of serum phospholipids as stabilizers of the serum lipid emulsion has recently been stressed in a study in which the particle size of lipid droplets in serum was related to the ratio between hydrophyllic and hydrophobic lipid concentration.[85] The implications of this thesis for studies on the pathogenesis of atherosclerosis has received support in the recent work of Ladd, Kellner and Correll[33, 34] which demonstrated a decreased incidence of experimental atherosclerosis in rabbits in the presence of a reduced ratio of cholesterol to phospholipid in the serum.

Gertler and his associates[86] examined the relationship of the serum cholesterol and phospholipids in normal individuals and in patients with

coronary heart disease. They found the mean serum cholesterol, phospholipids and the cholesterol/phospholipid ratio to be significantly higher in the coronary disease group compared to the control group. The increase in the cholesterol/phospholipid ratio in patients with coronary disease indicated a disproportionately greater elevation of serum cholesterol over phospholipids.

An interesting study regarding the relationship between serum lipids and skin xanthomata has recently been reported by Ahrens and Kunkel.[87] They found that in patients with primary biliary cirrhosis, the occurrence of skin xanthomata was directly related to the degree of elevation of the total serum lipids although there was a relatively normal cholesterol/phospholipid ratio in the serum. In these patients, however, there was no clinical, electrocardiographic or radiographic evidence of atherosclerosis or coronary disease. The factors which led to the formation of skin xanthomata, therefore, differed strikingly from those which determined the presence of atherosclerosis.

Fasting total serum lipids, lipid phosphorus and total cholesterol determinations were performed repeatedly by Eilert[88] on eleven female patients who received estrogens for various reasons. In all cases, there was a sharp reduction in the ratio of total cholesterol to lipid phosphorus during periods of hormone administration. The reduced ratio was usually attained by an elevation of serum lipid phosphorus and a fall in total cholesterol. This effect of the estrogenic hormones may in part explain the lower incidence of atherosclerosis in women under the age of forty years.

Further evidence regarding the relationship of cholesterol to other lipids of the serum might be found in the study of Duff and Payne[89] on alloxan diabetes in the rabbit. As stated above, this type of diabetes appeared to have an inhibitory effect on the development of experimental cholesterol atherosclerosis in the rabbit. The most consistent finding in alloxan diabetes of the rabbit was the presence of a greater proportion of neutral fat in relation to cholesterol than in the control animal.

Other Factors Affecting the Development of Atherosclerosis

1. *Obesity:* Based on observations on 1250 autopsies, Wilens[90] concluded that the occurrence of generalized atherosclerosis and of coronary atherosclerosis was directly proportional to the amount of adipose

tissue deposited throughout the body. In obese men, the incidence of severe generalized atherosclerosis was two and one-half times as great as in poorly nourished men. In obese women, the incidence of severe atherosclerosis was almost twice as high as in poorly nourished women. In a later investigation, Wilens[91] studied the relation of storage fat and of weight loss during terminal illness to atheromatous lesions in the aorta and in the main branches of the coronary arteries in patients between forty and sixty years of age. Less severe atherosclerotic changes were usually observed in patients with wasting diseases than in those without terminal weight loss. The author inferred, therefore, that significant resorption of previously formed atheromatous lesions may occur during periods of marked weight loss.

2. *Increased Filtration Pressure:* Moschcowitz[92] has stated that without increased intravascular pressure there can be no arteriosclerosis. This factor certainly cannot be implicated in all cases of arteriosclerosis since this lesion may occur without hypertension of any degree. Hueper[70] recognized the role of intravascular hydrostatic pressure on the development of atherosclerosis. He felt that the increased pressure whether local or general was followed by an ischemic anoxemia of the intima (with consequent increased permeability) due to compression of the vasa vasorum against the inelastic adventitia and to mechanical overextension of the contractile and elastic elements in the vascular walls.

In 1941, Bruger and Chassin[93] attempted to correlate the cholesterol content of the aorta and renal arteries with pre-existent arterial hypertension in human necropsy material. They confirmed the observation of Schönheimer[7, 94] that the cholesterol content of the human aorta increased with age. They showed, moreover, that the deposition of cholesterol in the thoracic aorta and renal arteries was greater in patients with hypertension than in subjects with normal blood pressure for the same age period.

Diet and Atherosclerosis

The influence of high or low cholesterol diets on the development or prevention of atherosclerosis in humans has received much attention in recent years. Although many papers have been written on this subject, the conclusions have been conflicting; certain highlights, however, might be reviewed.

In 1934, Rosenthal[95] collected and tabulated the data from twenty-

eight papers on the relationship of diet to atherosclerosis. The outstanding feature of his report was the finding that racial groups which consumed diets high in cholesterol and fat showed an increased incidence of atherosclerosis. Conversely, in those races (Japanese and Eskimos) where the intake of cholesterol and fat was low, atherosclerosis was not prevalent. Snapper[96] also reported on the low incidence of atherosclerosis in the Chinese who are known to consume a diet low in cholesterol. It may be argued that in these racial groups a hereditary factor may be at play. However, races which consume low cholesterol diets but have dissimilar hereditary backgrounds also show a low incidence of atherosclerosis, viz., Costa Ricans[97] and Okinawans.[98]

The effect of changing the dietary habits of members of these groups show interesting results. Javanese stewards on a luxury liner showed increased concentration of cholesterol in the blood when they consumed rich occidental foods.[96] In Egypt, Ismail[99] reported that among his private patients whose diets were similar to those of the Europeans, the incidence of atherosclerosis was high. On the other hand, in his hospital practice composed mainly of natives who consumed foods consisting largely of carbohydrate, the incidence of atherosclerosis was low. While these reports are interesting, it must be realized that they are not substantiated by adequate clinical and biochemical controls.

Several studies have attempted to correlate the level of cholesterol in the blood to the intake of cholesterol and fat in the diet. There is general agreement that the ingestion of a single meal high in cholesterol has no effect on the blood cholesterol of normal individuals. Blotner[100] confirmed this but reported a marked rise in the blood cholesterol level in obese individuals following the ingestion of a high fat meal (500 ml of light cream). These findings were not corroborated by the present authors;[101] they found that the total serum cholesterol of both normal and obese individuals was not affected by a high fat meal.

Of more interest and significance are the long term studies. Keys et al[102] studied the habitual diet of 482 normal men over a period of three years. These subjects were in an economic bracket which permitted full selection of diet. They were divided into age groups ranging from eighteen to fifty-five years of age and each group was further subdivided into low and high cholesterol intakes. Analysis of the results showed that the serum cholesterol level of this group of normal

men was not significantly related to differences in habitual cholesterol consumption ranging from 250 to 800 mg per day.

Wilkinson and his co-workers[103] examined eighty-three persons from a kindred in which essential familial hypercholesterolemia was present. These patients were allowed a free choice of diet. No relationship was found between the amount of carbohydrate, fat, protein and cholesterol in the diet and the level of total serum cholesterol. Delevett and one of us[104] noted no diminution in the cholesterol content of the blood in four patients with primary essential xanthomatosis who were consuming a diet low in cholesterol but normal in fat (vegetable fat) for several months.

Keys et al[102] reported that when the cholesterol and fat intake was severely restricted by a rice-fruit diet, a marked decrease in the serum cholesterol of patients with hypertension or idiopathic hypercholesterolemia was noted. Mellinkoff et al[105] observed a definite fall in the serum cholesterol of patients who were given a low cholesterol and low fat diet (protein hydrolysate and dextrimaltose) for benign lesions of the gastro-intestinal tract. Total calories consumed daily varied from 2200 to 2400; each patient either gained or maintained body weight on this regime. Hildreth et al[106] have recently reported that vegetable fats which are known to be cholesterol-free nevertheless increased the serum cholesterol of normal subjects who had subsisted on a low cholesterol and low fat diet. Gofman and his co-workers[82-84] have shown that the S_f 10 to 20 macromolecular bodies may be decreased in the blood following the ingestion of diets low in cholesterol and fat. This category of macromolecular bodies has been found in greatest concentration, as mentioned before, in individuals with hypercholesterolemia and in those young people who are predisposed to or suffer from coronary thrombosis.

These studies on the relationship of diet to serum cholesterol indicate that in order to decrease the concentration of cholesterol in serum, the habitual diet must have two characteristics, namely, (a) it must be free of cholesterol and (b) it must be low in both animal and vegetable fat.

Summary

The subjects of experimental cholesterol atherosclerosis and human atherosclerosis have been reviewed and their possible relationship dis-

cussed. Analysis of published data permits certain major conclusions: (a) The precipitation of cholesterol in the intima is accelerated by increased concentrations in the plasma of cholesterol, chylomicrons and macromolecular cholesterol aggregates of definite dimensions and by increased filtration pressure (hypertension) and generalized obesity; it is conceivable that some if not all of these atherogenic factors increase intimal permeability for cholesterol. (b) The precipitation of cholesterol in the intima is inhibited by such agents as estrogenic hormones, intravenous detergents, iodides, desiccated thyroid and thiocyanates; it is believed that these anti-atherogenic factors either maintain the colloidal stability of cholesterol in the plasma by increasing the concentration of plasma phospholipids or decrease intimal permeability for this sterol; the reputed anti-atherogenic activity of lipotropic factors such as choline, inositol and methionine has not been definitely established. (c) The prolonged consumption of foods low in fat and free of cholesterol may inhibit cholesterol deposition in the intima by decreasing the concentration in the plasma of cholesterol, chylomicrons and macromolecular cholesterol aggregates.

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ACTH AND CORTISONE AS THERAPEUTIC AGENTS IN ARTHRITIS AND SOME LOCOMOTOR DISORDERS†

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THE epochal contributions of Hench, Kendall, Slocumb and Polley on the administration of cortisone and ACTH in rheumatoid arthritis and rheumatic fever have inspired the most intensive and far-reaching clinical and fundamental studies in medicine.[1, 2, 3] At this relatively early stage of clinical trial and investigation of these substances few extensive series of cases have appeared, although many undoubtedly will be forthcoming steadily. We, therefore, present here a report of our experience with ACTH and cortisone in 128 cases of musculoskeletal disorders. These consisted of 72 patients with rheumatoid arthritis, 23 with rheumatoid-like diseases and 33 with non-rheumatoid musculoskeletal conditions.

Hench and his group have repeatedly emphasized the accomplishments of these compounds in demonstrating the reversibility of the rheumatic diseases.[1] In their studies they steadily have refrained from advocating a therapeutic role for the preparations. The great importance of ACTH and cortisone as versatile investigative tools is being reported with rapidly accumulating data in almost every other branch of medicine as well as in the rheumatic diseases.[2, 3, 4] The practical question that poses itself, at least in the field of rheumatic disorders, especially since the preparations have been released for general use, is: How effectively and safely can these compounds be applied as therapeutic agents? Our chief aim here is to present those of our own observations so far which may contribute toward an answer.

Their great potency for beneficial response and for undesirable reactions has been observed by us for only a little over one year, at this time. We, therefore, regard this report as a tentative, interim presenta-

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TABLE I.—METHOD OF ADMINISTRATION OF CORTISONE AND ACTH

1. *Preliminary Hospitalization* (In all cases.)
2. *Dosage*
   A. *Parenteral*
      1. Cortisone:—200-300 mg. I.M. for the first 24 hours (100 mg. every 8 hours); 150-200 mg. next 24 hours, then 100 mg. daily thereafter (50 mg. every 12 hours); in some cases 200 mg. daily until symptoms were adequately resolved; then the maintenance reduced gradually until sufficient for control of symptoms.
      2. Adrenocorticotropic Hormone:—100-150 mg. I.M. for the first 24 hours (25-37.5 mg. every 6 hours); 75-100 mg. next 24 hours, then 40-50 mg. daily (10-12.5 mg. every 6 hours); in some cases 80-100 mg. daily until symptoms adequately resolved; then a gradual reduction of maintenance dose level sufficient for control of symptoms.
   B. *Oral*
      1. Cortisone:—Same doses as parenteral, increased by 25 per cent if necessary; evenly divided 4 to 2 times a day.
3. *Ambulatory Follow-Up Plan*
   Both continuous and interrupted methods of administration investigated.

tion lacking the finality of the more extensive application and long follow-up so necessary for reliable therapeutic evaluation in the rheumatic disorders

Methods of Administration and Dosage: All of the patients in this series were hospitalized for 2-4 weeks for base-line studies and dosage regulation.* They were permitted to follow their usual habits of rest and ambulation. Supplementary analgesics were prescribed only for some individuals whose usual intake was permitted for observation on the relief of pain by ACTH and cortisone. These patients, as a rule, quickly requested that the analgesics be omitted.

A standard dosage schedule was followed in nearly all of the disorders according to the severity of the individual case. The usual dosage pattern is shown in Table I. The choice of either ACTH or cortisone was dictated generally by economic considerations, convenience of administration and the availability of each at the time. The oral tablet form of cortisone makes it a simple method of administration.[5] In our series the therapeutic effects of ACTH or cortisone were largely similar.

Control observations were made in two ways in the majority of

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patients with rheumatoid and rheumatoid-like arthritis, and in nearly everyone with a non-rheumatoid condition. A preliminary five to seven day period of thiamine chloride solution or of cholesterol suspension, given intramuscularly twice a day, usually was carried out at the beginning without informing the patient as to the nature of the medication. Placebo tablets were given for a similar time before oral cortisone. During the period of benefit repeated reduction of dosage and interruption of therapy provided further control observations on the relationship of the symptoms to the administration of ACTH and cortisone in the various entities under consideration.

Clinical Observations in Various Locomotor Disorders. Rheumatoid Arthritis: Improvement in our patients with this disease followed the pattern of responsiveness described by Hench and co-workers and others.[1, 5-10] Stiffness, pain and tenderness diminish in that order. Swelling is next to recede, but frequently does not resolve completely. Associated with these responses, increased ranges of motion usually become evident within a few days. In most cases coördinated motion is much more easily performed, even when mobility of the joints has not improved to any extent. This enhancement of coördinated movements, such as walking, getting up or down stairs, dressing, self-feeding, and many others, often is far greater than the effect on specific ranges of motion would indicate. Certainly the sense of well-being and relief from pain is remarkable, even in those patients who show little or no objective evidence of functional benefit. A unique and paradoxical effect in the therapy of rheumatoid disease is illustrated by many patients with impressive symptomatic relief who, nevertheless, may continue to show slight or even great joint swelling. Little or no remaining pain or tenderness and increased mobility frequently were observed in articulations still swollen and boggy, but without external signs of inflammation.

Evaluation of our results was based on the Therapeutic Criteria of the American Rheumatism Association.[11] Our figures reflect only their objective assessment (Table II). Of a series of seventy-two cases with rheumatoid arthritis at the time of this report, 44 per cent showed Grade I or Grade II improvement during the initial hospital period, with 4 per cent of the group in complete remission. Of the remainder, 54 per cent showed slight improvement; 2 per cent did not benefit. It must be added that the subjective improvement, at least during the

TABLE II.—RESULTS OF ADMINISTERING ACTH AND CORTISONE IN RHEUMATOID ARTHRITIS*

	Number of Cases	*Complete Remission (Grade 1)*	*Greatly Improved (Grade 2)*	*Slight Improvement (Grade 3)*	*None or Worse (Grade 4)*
Initial Short-Term Hospitalization, 10-30 days	72	3	29	39	1
		4%	40%	54%	2%
Ambulatory Maintenance, 30-340 days later	55	3	15	28	9
		5%	27%	51%	17%

* Evaluation of Response According to Therapeutic Criteria of the American Rheumatism Association.

initial periods, is in proportion to the objective response, sometimes greater.

In the follow-up period, fifty-five of the seventy-two cases had been receiving maintenance doses for a period of one month to a year at the time these figures were completed. In these patients an attempt was made to use doses sufficient for at least tolerable control of the symptoms without provoking side-effects or complications. As seen in Table II, there was a somewhat greater number of poor results in the follow-up period, when 17 per cent showed no response or became worse, while only 27 per cent were greatly improved. The three patients who went into complete remission during their hospital stay remained symptom-free for four to seven weeks. The number of cases showing slight improvement was almost identical during the initial hospitalization and the later maintenance period.

A further breakdown of our findings in this limited series cannot be described in detail here. It may be stated in brief that the more advanced cases with structural changes of Stage III and IV and those with functional impairment of Class III and IV responded the poorest and appear to be the least likely to show the desirable Grade I or II improvement.[11] These observations agree with those of Boland.[5] The large number of such late and severe cases in our series accounts for the less favorable figures in our report.

The grades of response shown in Table II obviously do not reflect any specific curative action. Appreciable degrees of improvement, subjective and objective, certainly are produced more rapidly, more frequently and more consistently than by any other therapeutic measure for rheumatoid disease. Unfortunately, the symptoms returned within days or weeks, and rarely in months, when rest periods without the compounds were instituted. To control manifestations of rheumatoid activity during maintenance therapy, short periods of booster doses to overcome "rebound" symptoms often become necessary.

Follow-up assessment of response in patients kept on maintenance doses for a month to almost a year, showed rather favorable consistency of responsiveness (Table II). In several instances a change from one compound to the other overcame resistance of symptoms or eliminated annoying side-effects. In three cases with refractory symptoms both substances proved ineffective in due time. Two other patients showed similar undesirable reactions to the preparations, contraindicating their further use. Patients who interrupted treatment for rest periods, or discontinued it entirely for economic reasons, sometimes developed more severe and more disabling symptoms than those originally presented. Since these figures were assembled, and larger numbers of our patients on longer-term therapy have accumulated, there has been a gradual increase of cases refractory to these compounds. Some others have required steadily increasing amounts to maintain control over the symptoms.

Rheumatoid-Like Musculoskeletal Disorders:[1-4] Seven cases of ankylosing spondylitis received ACTH or cortisone (Table III). All experienced some relief of pain and stiffness. Three of the patients were greatly improved, with increased motion and enhanced functional capacity. Four showed only slight but definite benefit.

The joint manifestations in four cases of psoriasis with arthropathy were greatly improved in the early phases of therapy (Table III). Two of these subsequently have run a fluctuating course. The skin lesions tended to respond at first, but they soon returned to their former state in two of the patients. In a third the cutaneous eruption became worse on doses adequate to control the arthritis symptoms.

One case of non-specific ulcerative colitis with arthropathy responded well to ACTH in the articular and colonic symptoms as well as in the changes observed by proctoscopy (Table III). When the

TABLE III.—RESULTS IN RHEUMATOID-LIKE DISEASES

	No. Cases	*ACTH*	*Cort.*	*Over-all Improvement** *Great*	*Slight*	*None*	*Worse*
Ankylosing Spondylitis	6	1 (1 both)	5	3	3		
Psoriatic Arthropathy	4	2 (1 both)	2	4			
Gouty							
Acute	2	2		2			
Chronic	4	2 (1 both)	2	1	2		
Ulcerative Colitis with Arthritis	1	1		1			
Collagen Diseases	3	2	1	1	2 (all short-term observations)		

* No complete remissions, except in Ac. Gout.

medication was discontinued, however, the clinical features were reactivated within a few weeks.

The joint symptoms and signs in all of the rheumatoid-like disorders exhibited a pattern of response approximately similar to that of rheumatoid arthritis, and the same tendency toward inevitable recurrence of the active clinical picture when administration of the compounds was interrupted.

Collagen Diseases: Three cases with different collagen diseases in an early stage were studied during an initial hospital period: scleroderma (1), disseminated lupus erythematosis (1) and dermatomyositis (1) (Table III). Joint symptoms were present in all. In the case of scleroderma the articular signs, as well as other manifestations, were greatly improved. Only moderate benefit was noted in the other two. In each of these patients there was appreciable relief of pain and stiffness as well as resolution of joint swelling.

Gout: Two patients with acute exacerbations of gout were quickly relieved by ACTH. In 2 cases of chronic gouty arthritis, on maintenance doses to relieve mild continuous symptoms and to prevent attacks, only slight benefit was provided by cortisone. One of these cases of acute

gout did not respond to full doses of colchicine, but was relieved rapidly when cortisone was given.

ACTH or cortisone apparently may serve a useful role in suppressing the acute attacks of gout in the occasional patient who becomes unresponsive to colchicine. Whether these hormones may be employed effectively and safely to prevent and dissolve tophaceous deposits by increasing the urinary elimination of uric acid over a long period of time can only be decided by prolonged and careful study in a sizeable group of patients with varied degrees of involvement.

Non-Rheumatoid Musculoskeletal Conditons.[1-4] *Degenerative Arthritis of the Hip:* Ten cases of osteoarthritis of the hip were studied (Table IV). These were patients with advanced changes presenting a troublesome degree of pain and stiffness and marked limitation of motion. They were a selected group chosen chiefly for the severity of involvement, with practically no joint space demonstrable in the films of any but one. It did not seem possible at the outset to bring about any perceptible increase in their ranges of motion. Nearly every case had been screened by the orthopedic department and approved for investigative therapy as a serious problem. One of the ten cases was not benefited. Nine patients with extensive unilateral or bilateral hip degeneration were relieved of pain to a significant degree or entirely. Only one of our ten cases showed significant increase of motion at the affected hip and this has been sustained by maintenance doses for two months.

Improvement following ACTH and cortisone in these individuals usually was evidenced by great relief of pain, a generally and locally diminished feeling of stiffness, and better coördination of mobility. Patients could rise from a sitting position more easily and they could go up and down stairs more readily. Comparatively small daily average doses of these hormones (12.5 mg. to 50 mg.), given every one to three days, were adequate to maintain an initially favorable effect, except in the most painful cases. During rest periods without the compound, the symptoms invariably recurred. One of the patients has been under more or less continuous and satisfactory maintenance for eight months by taking 25-50 mg. a day, without any adverse reactions so far.

Reflex Dystrophy, the Shoulder-Hand Syndrome: Of ten cases of reflex dystrophy of the upper extremity (shoulder-hand syndrome) four were treated with ACTH, five with cortisone and one with both. Of this series only one was in Stage I, while the rest were more advanced.

TABLE IV.—RESULTS IN NON-RHEUMATOID CONDITIONS

	No. Cases	*ACTH*	*Cort.*	*Complete*	*Over-all Improvement Great*	*Slight*	*None*
Degenerative Arthritis (Hip)	10	2	8		1	8	1
Shoulder-Hand Syndrome (Reflex Dystrophy)	10	4 (1 both)	6	1	5	2	2
Periarthritis of Shoulder	10*	4 (1 both)	6		6	1	3
Calcific Tendinitis and "Bursitis" of Shoulder							
Acute	1		1	1			
Chronic	1		1		1		
Trigger Finger	2	1	1				2

* Manipulation under anesthesia in 5 cases.

Each of the patients had received previous treatment with physiotherapy, manipulative therapy or local and stellate ganglion blocks without significant improvement.

As seen in Table IV, one patient's symptoms were completely abolished and in five they were greatly improved. Three cases showed slight improvement and one did not respond at all. Pain and vasomotor disturbances were quickly influenced. Within a few days to two weeks, pain and swelling were lessened or eliminated, and in some cases abnormalities of temperature, color and sudomotor activity of the hand tended to recede quickly. Limitation of motion at the shoulder responded sooner than at the hand in most instances, including those of long standing. Some of the cases improved further during the follow-up period up to nine months later.

During the initial hospital stay the dosage requirements for rapid control of pain and mobilization of the parts were greater than in rheumatoid arthritis, an average of 200 mg. of cortisone daily or 75-100 mg. of ACTH a day. Maintenance therapy was needed to sustain the effects. At this time only two of this group, after one to six months of con-

tinuing doses with trial rest periods, still take cortisone to control recurring symptoms when administration is interrupted. There has been no deterioration in the improvement of any of these individuals during two to nine months of follow-up, seven having been observed for two to seven months since maintenance doses were stopped. It is of interest that two of these patients had failed to respond to sympathetic blocks. The contractures already present in most of the responsive cases in this group were uninfluenced by ACTH or cortisone.

Periarthritis of the Shoulder (*"Frozen Shoulder"*): In ten cases of periarthritis (periarticular fibrositis) of the shoulder we administered cortisone or ACTH, or both (Table IV). Seven of the patients were started on these substances and another three received them after manipulation. Of the seven cases given either or both of these compounds only, all reported definite to complete relief of pain. One of the seven showed a complete response, two others great improvement, one slight improvement and the remaining three no functional improvement in spite of relief of pain.

Five patients were subjected to manipulation of the extremity under anesthesia. Three of these previously had failed to respond adequately to cortisone and/or ACTH after a period of several weeks of large doses. They were manipulated during administration of the drug which was continued for varying periods of time. In the other two manipulations, therapy with these substances was initiated following this procedure, four days to three weeks afterwards. Three of the 5 cases of combined manipulation with steroid therapy were greatly benefited, one slightly and another not at all. As with the "shoulder-hand" cases, in periarthritis of the shoulder larger doses of ACTH and cortisone were required for the first seven to ten days than in rheumatoid arthritis. It was necessary to keep these patients on maintenance doses for one to three months to "fix" the good effects of manipulation. Attempts to discontinue the cortisone during this maintenance period were followed quickly by recurring pain and disability. Follow-up of the recoveries in this group three to eight months after terminating maintenance doses has revealed no recurrences except an occasional ache in the affected shoulder in two cases.

Calcific Tendinitis and Bursitis of the Shoulder: Only two patients suffering from these conditions have been treated by us up to this time. In one case with typical acute calcific tendinitis (supraspinatus), pos-

sibly with secondary subdeltoid bursitis, pain was abolished within twenty-four hours and severe disability greatly resolved within seventy-two hours after cortisone was started on the same schedule used in rheumatoid arthritis. The calcium deposit remained after the symptoms had subsided. This acute disorder usually is of brief, if stormy, duration and, therefore, would require a good-sized series to confirm the contribution of the steroid.

In one patient with chronic calcific tendinitis of two years' duration, probably associated with some periarthritis, uncomfortable mobility, more or less continuous pain and tenderness to palpation were greatly improved within seven days. They still were almost entirely banished "most of the time" during two months of maintenance dosage and observation thereafter. The calcific deposits were not changed.

Trigger Finger: Two cases of constrictive tendovaginitis ("trigger finger") were treated with completely negative results. Both occurred coincidentally in patients with responsive rheumatoid arthritis. The tendon lesions were of long standing. It is possible that early disorders of this nature might prove more amenable to these agents.

Orthopedic Procedures With ACTH and Cortisone. Surgery: The reports by Ragan and coworkers[7] on the delayed healing of wounds in patients and in experimental animals receiving cortisone or ACTH has raised the question as to whether these substances consistently produce these effects clinically and whether they should be discontinued in individuals who are to undergo orthopedic or other surgical procedures. We have had occasion to observe the healing of surgical incisions in six patients while they were receiving average doses of ACTH or cortisone.

Two arthrotomies proceeded to normal recovery without incident. Three local incisions consisting of two biopsies and one drainage of an abscess also healed as usual during steroid therapy. One patient with rheumatoid arthritis was subjected to a bilateral bunion operation with the additional removal of a subcutaneous nodule on each hand, without interruption of previously administered cortisone during her surgery. The compound was temporarily discontinued five days postoperatively, because two of the four operative sites continued to ooze.

Evidently, healing of some minor incisions is not retarded by the use of cortisone and ACTH. During such therapy, it appears that the extent of the wound, its location, the amount of compound employed,

and the time elapsed after surgery may be important factors in wound healing not reflected in our small number of cases.

Contractures and Post-Manipulation Use of ACTH and Cortisone: The effects of cortisone and ACTH on the correction of joint contractures, especially in rheumatoid arthritis, are under study at the present time. These compounds seem to be effective in producing mobility in many of these cases without supplementary aids. In others they appear to provide sufficient control of pain, inflammation and spasm to permit active and helpful use of orthopedic measures and physical modalities previously not tolerated. Sufficient time has not elapsed for an exact delineation of their place and contribution to these procedures, promising as they appear at this point.

The combined use of ACTH or cortisone with manipulative measures was helpful in some of the patients in our small group with periarthritis of the shoulder. It is possible that a similar application at other sites also may prove useful.

Side-Effects and Complications of ACTH and Cortisone: Throughout these chapters there have been references to the beneficial and, in general, remarkable effects of ACTH and cortisone, even when only temporary, in a broad group of musculoskeletal disorders. A balanced discussion of these substances must include some consideration of the "side-effects" and complications they may produce.[12] We have reserved the term "complications" for those pathologic states appearing during the administration of ACTH or cortisone which are not reversible following discontinuation of therapy, or those side-actions of the compounds which constitute a threat to the patient's well-being or survival.

In our 128 cases, during short and long-term administration we have observed a variety of side-effects and complications (Table V). The large number of such reactions noted here was due to multiple incidents in some cases. They appeared in about 40 per cent of the patients in our series and about 90 per cent of them were temporary, quickly reversible or of no clinical importance.

Glycosuria occurred in eighteen cases. It was transient in sixteen but remained in only two when the drug was discontinued. It would seem that the two instances of persistent glycosuria represented latent diabetes activated by treatment. Edema appeared in sixteen patients, and in half of them it necessitated mercurial diuretics. Rounding of the face and body developed in twelve cases, and became more frequent and

TABLE V.—SIDE-EFFECTS AND COMPLICATIONS OF ACTH AND CORTISONE IN 128 CASES DURING SHORT AND LONG TERM ADMINISTRATION

Metabolic	
Glycosuria (transient in 16)	18
Edema (peripheral)	16
Rounding of face and body	12
Cutaneous	
Hirsutism	9
Acne	8
Miscellaneous eruptions	6
Purpuric eruptions	4
Striae	2
Pigmentation of nails	1
Menstrual Disorders	4
Gastrointestinal	
Perforation of ulcer (duodenal)	1
Constipation	4
Abdominal cramps (ACTH)	2
Unclassified	2
Psychic abnormalities	
Euphoria	14
Psychotic symptoms	7
Insomnia	4
Cardiovascular	
Hypertension (transient)	5
Congestive failure	1
Coronary insufficiency	1
Hemiplegia (transient)	1
Peripheral arterial occlusion	1
Thrombophlebitis	7
Neuropathic	6
Skeletal (Osteoporosis)	
Vertebral compression syndrome	1
Fracture	1

more pronounced on long-term therapy.

Cutaneous reactions were noted in thirty individuals. They consisted of hirsutism, diffuse or circumscribed eruptions particularly erythematous, acneform lesions, purpuric eruptions and striae. One case showed pigmentation of the nails.

Disorders of menstruation occurred four times. There were two instances of impotence in males; also increased libido in one other male and in one female.

Gastrointestinal disorders were observed seven times. Perforation of a duodenal ulcer occurred in one patient on ACTH before admission to our service. Two patients suffered abdominal cramps during administration of ACTH with the earlier preparations. Four complained of severe constipation under cortisone.

Psychic features developed in twenty-four patients and consisted of euphoria in fourteen instances, severe insomnia in four. In seven patients psychotic symptoms occurred at one time or another during

treatment, but they were temporary, disappearing soon after the compound was stopped.

Cardiovascular and peripheral vascular manifestations arose during therapy in 16 of the series. Five patients developed hypertension of a transient nature which disappeared while the compound was continued. Symptoms of coronary insufficiency and mild congestive failure set in during cortisone administration to one patient who had suffered from such attacks previous to this therapy.

Other vascular reactions occurred in ten patients. Seven developed thrombophlebitis, another a bilateral femoral arterial occlusion. An additional patient suffered a transient hemiplegia followed, soon after resumption of cortisone administration for severe recurrence of polyarthritis, by a cerebral thrombosis, signs of diffuse encephalopathy and a gradual downhill course and fatal termination. All but one of the individuals who developed vascular complications were in the older age groups (sixth to eighth decade). It is quite possible that many of the peripheral circulatory and cardiovascular complications occurring with the use of ACTH and cortisone, which will be attributed to them, represent unrelated coincidental events. In our own series we believe, however, that the frequency of vascular complications suggests that they are more than chance occurrences. A more extensive experience is required to interpret the association of these ominous developments.

Neuropathic symptoms arose in six patients. Two complained of paresthesias in the hands and feet which vanished when the dose was decreased or stopped. Two others developed a paresis of the extensor muscles of the third and fourth fingers of one hand. The fifth patient was annoyed by neuritic symptoms along the ulnar distribution of one hand. In one of the cases a gradual loss of smell was noticed by her after two months on cortisone. Apparently complete anosmia and some disturbance of taste has continued during six months of therapy. Although peripheral neuropathies are sometimes encountered in rheumatoid arthritis, the frequency of these disturbances in our series is higher than we ordinarily would expect. Severe asthenia and weakness developed during treatment in three of our patients and, after cortisone was discontinued, in two other patients and in one on ACTH.

One of the most troublesome complications of cortisone and ACTH therapy is the production of demineralization of bone, or the aggravation of preëxisting osteoporosis. The difficulties of this problem in

patients requiring long-term therapy were exemplified in our series by two mishaps associated with increased osteoporosis. One patient without previous spinal symptoms presented acute dorsolumbar back pain with the clinical picture of a compression fracture of the 11th dorsal vertebra during prolonged and greatly helpful cortisone therapy for severe rheumatoid arthritis. In the second patient a pathologic fracture through the surgical neck of the humerus occurred while she was on cortisone for periarthritis of the shoulder. She had made a good recovery during an initial course in the hospital and had been home at the time for three weeks on maintenance doses. While passing through a doorway, the patient just "brushed" the door-frame. She suffered pain which was not severe, but out of proportion to the nature of the injury. X-ray films revealed the unexpected fracture and increased osteoporosis of the upper end of the humerus.

The propensity of these compounds for certain side-effects amply discussed in the literature, and their apparent tendency to be associated with other serious side-actions and complications suggested in our series, emphasize the importance of the contraindications and precautions to be observed in their use. These will not be considered here.

Discussion

ACTH and cortisone produce impressive beneficial effects in a variety of arthritic and other locomotor conditions. The versatility of these compounds is evidenced by their influence on symptom-producing mechanisms of such varied origin as inflammatory processes (rheumatoid and rheumatoid-like); degenerative (secondary fibroplastic?); metabolic (gout); irritative (?); traumatic and/or metabolic (?) (periarthritis, calcific tendonitis); and neurovascular (?) (shoulder-hand syndrome). The questions that repeatedly presented themselves during these observations were: Do these favorable musculoskeletal results depend on some effect in the peripheral tissues common to all of these diseases and disorders of the supportive structures? On the contrary do the benefits merely reflect the multiple action of the hormones in various forms of pathophysiology or pathology, exerting one or more of a variety of specific activities in different disturbances?

The predominant clinical effects of these compounds in musculoskeletal disorders from present clinical observations may be summarized as anti-inflammatory, analgesic, antipyretic, anti-allergic, anti-fibro-

blastic and the altered permeability of tissue membranes. These characteristic actions are so varied as to explain broadly the therapeutic results obtained. The more exact manner in which the preparations, or those substances into which they are transformed or which they produce, bring about control of symptoms has not been clarified as yet. Whether a central and a peripheral effect, or the latter alone accounts for the outcome, and how, remain to be settled.

ACTH and cortisone are among the most powerful agents yet used in the study and treatment of disease. Their remarkable therapeutic activity in suppressing the symptoms of musculoskeletal disease, unfortunately, is associated with a potential for disconcerting and serious side-effects and reactions. Certainly, increasing side-actions and complications during the use of ACTH and cortisone continue to be observed. These represent chiefly the clinically perceptible reactions during the rather limited time these substances have been utilized. A thorough assessment of the place of ACTH and cortisone as therapeutic agents, therefore, cannot be made until enough time has elapsed to give us a better understanding of the full range and circumstances of the reactions to these compounds.

For such an evaluation it also is necessary to know the tissue changes they provoke, if any, which possibly are not clinically or pathologically recognizable for a longer period than our present experience. Such information and a fuller comprehension of the effects of these compounds, it is to be hoped, may permit us to develop improved techniques for their administration or combination with other substances, and for the control of undesirable reactions.

Summary and Conclusions

1. In seventy-two patients with rheumatoid arthritis and in a small group with rheumatoid-like inflammatory joint disease, ACTH and cortisone provided the most rapid, predictable and effective suppression of symptoms of any agent so far available.

2. These results occurred to some degree in nearly all patients with rheumatoid arthritis and were sustained with maintenance doses in the great majority of the cases, although a gradually increasing number of individuals became refractory or developed troublesome rebound symptoms and undesirable side-effects or complications as the maintenance periods grew longer.

3. In degenerative arthritis of the hip, of sufficient severity to warrant the use of such powerful agents, appreciable benefit of lesser or greater degree was provided by these compounds in nine of ten cases. In two patients who received maintenance doses, relatively small amounts have continued the benefits for long periods.

4. In small groups of non-rheumatoid locomotor disorders—reflex dystrophy (shoulder-hand syndrome) and periarthritis of the shoulder ("frozen shoulder"), impressive control of symptoms or recovery was associated with the use of ACTH and cortisone. Relatively short maintenance periods were required to sustain the effects until the compound could be discontinued entirely without return of symptoms.

5. Approximately one-third of the patients (40) in this series of 128 developed benign or unpleasant side-effects and a small number of important complications. The most serious or troublesome of these were the vascular incidents, the psychotic reactions, the neuropathies and the fractures.

6. Our results confirm the original observations that ACTH and cortisone provide the most powerful suppressive action yet observed in chronic inflammatory joint disease, and that this effect often may be prolonged over indefinite periods with maintenance doses.

7. The beneficial action of these compounds in such often self-arresting conditions as shoulder-hand syndrome and periarthritis of the shoulder in our small groups of cases suggests that application of ACTH and cortisone in the comparatively short periods of administration required to effect or to accelerate improvement in such acute or chronic self-limiting disorders is worthy of more extensive investigation.

8. In view of the comparatively short period these powerful substances have been available and the probable incompleteness of our information regarding the full range of clinical and pathological changes to be expected, particularly during long-term administration in chronic articular disease, evaluation of ACTH and cortisone as practical therapeutic agents must be deferred at this time.

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RECOMMENDATIONS FOR ACTION TO RELIEVE THE NURSING SHORTAGE

THE nurse shortage in this country is a matter dating back to many years before World War II. It will undoubtedly become aggravated as more and more nurses are absorbed into the armed forces. The Committee on Public Health Relations of The Academy has given close attention to this problem and has issued various recommendations designed to alleviate the crisis. The Committee has emphasized especially the importance of enlarging the role of practical nurses in the care of the sick and has supported efforts to improve the quality of their training.

Within recent months the Interdepartmental Health Council of New York State, representing the State Departments of Health, Mental Hygiene, Social Welfare and Education, has promulgated, through an Advisory Committee on Nursing Service, a set of proposals for the organization of nursing education and service. These proposals embody changes that have aroused deep concern on the part of practicing physicians and hospital administrators. Since neither of these groups was represented on the committee that formulated the report, the Committee on Public Health Relations examined the proposals from these points of view.

The Interdepartmental Health Council proposes that only two types of nurses be recognized: 1) diploma nurses, licensed after two years of training in technical courses, and 2) college degree nurses, prepared in a four-year course and eligible for graduate training to fill positions as educators, supervisors and administrators. It is suggested that degree nurses be used to provide nursing care in complicated clinical situations and "to act as team captains for planning and directing and giving personal nursing care to individuals and groups, and to fill first level public health positions." To carry out the nontechnical duties associated with nursing care, the Council proposes "nursing aides" trained either on the job or in special courses in secondary schools. Aides might receive certificates but would not be licensed.

The proposals make no provision for practical nurses. They suggest instead that the training courses for practical nurses be merged with the standard three-year nursing course to produce in two years the "diploma

nurse." They recommend that high school graduation be required of all candidates for nurse training. The Academy Committee is of the opinion that such a requirement would eliminate many older women who have not graduated from high school as well as many younger women who would make competent practical nurses.

A further radical change suggested in the proposals is the transfer of all basic training from hospitals to academic institutions. Diploma nurses would be trained in "postsecondary" schools, such as technical institutes, junior and community colleges, while degree nurses would take their work in institutions of higher education.

While the presentation of basic training for nurses in schools and colleges rather than hospitals may have advantages, the Committee wishes to point out that hospital schools of nursing have for many years turned out competent nurses and that no evidence has been offered to show that they are not still doing so. Although some schools are not up to the highest standards, this is no reason for discontinuing all of them. Furthermore, the Committee is unable to accept the Council's theory that placing the training of nurses in academic institutions would strengthen the appeal of nursing as a career; the opportunity for service still exerts an influence upon the choice of nursing as a vocation. The Joint Committee on Nursing Education and Service of the Greater New York Hospital Association and the Hospital Association of New York State is of the opinion that hospital schools can adjust their curricula wherever necessary and that they can adequately train nurses in two years without radical changes or very expensive additions. If experimental programs are to be set up, hospital schools should participate in them.

To implement the suggested schemes of education, the State Interdepartmental Health Council makes a number of proposals for action. First, it urges the provision of governmental subsidies to pay for the training of nurses. It recommends amendment of the Nurse Practice Act to delete the present requirement that all nurses applying for licensure be 20 years of age. At present young women entering upon nurse training, when they graduate from high school are in many instances, particularly in the case of practical nurses, still under the age limit for licensure when they complete their studies and are thus unable to begin the practice of their vocation, sometimes for more than a year.

Other proposals relate to demonstration programs for the training in appropriate educational institutions of the three types of nursing

personnel—diploma nurses, degree nurses and nursing aides; to analysis and evaluation of the various factors in nursing service, and to the improvement of nursing care through official and voluntary public health nursing services.

The Committee recognizes that these are long-range proposals and takes cognizance of the Council's statement that the proposed plans would "affect neither the status of those nurses now in practice nor the existing pattern of nurse education during the experimental and developmental stages, which period may require considerable time." Long-range planning and experimentation to resolve the problem are desirable, but something has to be done to meet the present critical situation. It is therefore the opinion of The New York Academy of Medicine that steps should be initiated by the State Department of Education, with the aid of local bodies, to plan a legislative and administrative program for early action. The Committee submitted to the State Commissioner of Education a statement of points to be considered in conjunction with such a program:

1. The age at which young women may enter upon active nurse practice should by legislative act be reduced from 20 to 18.

2. Nurses not licensed in this State should be permitted by legislative act to serve on the nursing staffs of hospitals under supervision in the same manner as interns are now permitted to serve before they are licensed to practice.

3. The training of practical nurses should be continued, and any effort to abolish such training should be vigorously opposed. The schools for practical nursing should be developed to fulfill the need for competent people to take care of patients with nonacute conditions and to provide for the care of those with long-drawn-out maladies or in the convalescent stage of illness. The practical nurse has established a secure place for herself in the care of the sick, both in their homes and in the hospitals.

4. The Academy stands opposed to the proposal that all candidates for nurse training should be high school graduates. Such a requirement would automatically eliminate some of the most valuable sources of practical nurse power, young or middle-aged women with a talent for nursing, who have not finished high school. Many capable women, who for some reason have not completed an academic high school course, are well able as practical nurses to give simple care to the sick under the supervision

of a physician or a graduate nurse. This reservoir of potential nursing service must not be ignored—the country needs all the nurses that can be mustered.

5. Changes in procedure are recommended, to permit that all necessary instruction in nursing be completed within the statutory two years and that the third year be devoted, as it were, to an internship on a salary basis. This would make available to the hospitals a great deal of the time of the third year, which now includes class work.

6. All training schools should be alerted to the possibility that a two-year course may supersede the present course and should be requested to make the necessary adjustments in their curricula.

7. Every effort should be made to stimulate nurse recruitment. The proposed reduction of the course from three to two years, with the opportunity for those who so desire to obtain additional specialized instruction in clinical or administrative phases of nursing at educational institutions, will appeal to young women who are responding to nursing as a vocation, first, because of the opportunity it offers for service, and secondly, because of the educational status it affords for those who elect a degree in nursing. Every resource for adequate training of nurses should be availed of. Joint nurse-training programs for hospitals of a given region, if they desire to participate, should be encouraged.

The Commissioner of Education responded to this communication with an expression of appreciation for the serious consideration given to the problem by the Committee on Public Health Relations. He stated that the Department of Education is already creating experimental programs for the study of the proposed course and informed the Committee that the suggestion for internships in nursing is under consideration. With respect to the position of the practical nurse, the Commissioner made the following statement: "Irrespective of any adjustment that may take place in the nursing profession, it is clear that we must provide for a type of nursing service that is on a different level from that provided by the registered nurse."

The time for leisurely discussion is past. Those responsible for administrative changes in nursing education should make the necessary preparations to act without delay in this emergency.

SUBCOMMITTEE ON NURSING OF THE COMMITTEE ON PUBLIC HEALTH RELATIONS*

Oswald R. Jones, M.D., *Chairman* Beverly C. Smith, M.D.
Harvey B. Matthews, M.D. E. H. L. Corwin, Ph.D., *Secretary*

* Recommendations approved by the Committee on Public Health Relations, May 7, 1951.

SECTION ON MICROBIOLOGY

WEDNESDAY EVENING, FEBRUARY 25, 1951, AT 8:30 O'CLOCK

*Studies on the Mechanism of the Toxic Action of Newcastle Disease Virus**

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Toxic action has been ascribed to relatively few viruses. In fact, only the influenza[1-3] and lymphogranuloma-psittacosis[4] groups of viruses have been adequately demonstrated to produce such effects. In general, the toxic manifestations of these viruses have been widespread, and the course of production of local lesions has not been convenient to study. Therefore, when it was observed that the intranasal inoculation of Newcastle disease virus (NDV) infected allantoic fluid in the mouse produced extensive pulmonary consolidation, often followed by death, in the absence of demonstrable virus multiplication, a detailed study of the mechanism of this toxic action was undertaken. It is the purpose of this paper to report the results of experiments which indicate that the toxic effect of NDV is associated with a series of events similar to those which are thought to occur in the initiation of a virus infection.

It was not possible either to produce lesions or to pass infectious NDV in series in the mouse lung. When mice were inoculated intranasally with NDV, and groups were killed at daily intervals in order to determine the concentration of infectious virus in the lungs by titration in the chick embryo, it was found that a progressive decrease in concentration of infectious virus occurred at an average rate of 0.93 log unit per day. However, as the concentration of infectious NDV decreased, the extent of the pulmonary consolidation in the same mice increased, and reached maximal degree between the third and fourth days after viral inoculation.

Neutralization experiments with potent homologous and heterologous immune sera clearly demonstrated that NDV was responsible for the extensive lesions produced by the infected allantoic fluid. Extensive experiments revealed that the lesion production factor and infectious virus particle were adsorbed to and eluted from chicken red blood cells at a similar rate and to a similar degree. In addition, the lesion production factor sedimented with the virus particles in high gravitational fields. These data clearly indicated that the toxic property is a function of the Newcastle disease virus particle *per se*. Experiments in which infectious NDV was exposed either to ultraviolet irradiation or heat, and the inactivation of the properties of infectivity and toxicity followed with time, have demonstrated that the production of pulmonary consolidation in the mouse is dependent on the fully infectious virus particle. These findings led to the postulate that lesions are produced with NDV in the lungs of mice by a mechanism similar to that involved in the initiation of a pneumotropic virus infection.

The first essential step in production of lung lesions by NDV appears to be host cell-virus combination. When the receptor-destroying enzyme (RDE) from *Vibrio cholerae* culture filtrate[5] was injected intranasally into

mice six hours before 10^6 E.I.D. of Newcastle disease virus, the production of lung lesions was completely prevented. Heated RDE and broth had no preventive effect.

Combination of NDV with the living mouse cells is rapid and, in so far as determinable, irreversible. As in an actual virus infection, immune serum injected either before or with NDV prevented formation of pulmonary lesions, but when immune serum was injected five or fifteen minutes after virus the pulmonic consolidation was not prevented although it was significantly limited in extent. Injection of serum thirty minutes after viral inoculation had no effect on lesion production, and the degree of pulmonary consolidation was the same as when normal serum was injected after virus.

Production of toxic lesions by NDV appears to be dependent not only upon host cell-virus combination, but also upon one or more reactions which occur within the host cell in a manner similar to an actual viral infection. A strain of influenza A virus, which failed to produce lesions in the mouse lung but multiplied extensively in this organ, when inoculated intranasally three days before NDV, interfered with the production of lung lesions. Present evidence[6-9] indicates that interference with the multiplication of one virus by another is the result of a reaction between the first virus and the host cell which depletes the cell of a substance or metabolic system required by the second agent for multiplication.

The evidence obtained indicates that: production of lung lesions with NDV is a function of the fully infectious virus particles; NDV particles react with susceptible lung cells in a manner identical with that of virus particles capable of initiating an actual virus infection; despite the steps traversed by NDV in reactions with the lung cells, newly formed infectious virus particles are not demonstrable.

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*Studies on the Relationship between the Theiler Group of Viruses and the Intestinal Tract of the Mouse**

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Following Theiler's[1] isolation of the virus which causes spontaneous encephalomyelitis in mice, it was shown by Olitsky[2] that this virus is present in the intestinal tract of almost all young adult mice. Olitsky[3] also reported that the virus, which he named the TO strain, is consistently absent from the intestines of mice younger than twelve days of age. Subsequently, Theiler and Gard[4] isolated the GD VII and FA strains of mouse encephalomyelitis virus. These latter viruses are not known to be present in the intestinal tract and are maintained by intracerebral passage in mice. Relative to the TO virus, these 2 strains are very virulent.

The purpose of this preliminary report is to present the results of two studies: (a) the isolation from adult mouse intestine of an inhibitor against the GD VII virus; (b) a comparison of the susceptibilities of mouse intestine and mouse central nervous system (CNS) to infection with the TO virus.

Isolation of the GD VII Inhibitor:—In the course of experiments with the GD VII virus, it had been observed that if virus is added to a mince of washed adult mouse intestine, there was a marked reduction in the infectivity titre of the virus. This observation was studied in greater detail with the following results: 1) If a water or saline extract of the tissue was used, a similar effect was obtained. 2) The inhibitory substance was found to be heat stable, non-dialyzable, insoluble in organic solvents such as acetone, ether, and chloroform.

The purification of the inhibitor was undertaken. Preliminary experiments indicated that the inhibitory activity was associated with the polysaccharide fraction of the crude tissue extracts. The commonly used methods for polysaccharide purification were therefore followed to isolate the inhibitor. In essence, the method involves the removal of lipids by acetone and ether, removal of proteins by precipitation with trichloracetic acid followed by denaturation of the residual protein by shaking with chloroform, removal of nucleic acids by precipitation with $CuSO_4$, and precipitation of the polysaccharide with ethyl alcohol.

In order to determine the effectiveness of the method, aliquots were collected after each step and the inhibitory activity determined. In the early stages of this problem, inhibitor activity was measured by in vivo titrations. For this purpose, Gard's[4] method for measuring virus titre, expressed as the $\frac{1}{T}$ value, was used. The activity was estimated by the reduction in the $\frac{1}{T}$ value produced by the inhibitor.

Lahelle and Horsfall[5] described a method for measuring the GD VII virus titre based on the agglutination of human erythrocytes by the virus. It was found that the intestinal inhibitor was effective in inhibiting hemagglutination as well as infectivity, and that this property can be used for the quantitative determination of the inhibitor. This technique was found to be not only more rapid, but also more quantitative than the in vivo method.

Wherever practicable, specific activity was determined in terms of hemagglutination-inhibition units per gram of dry weight. As an illustration of the data obtained, a protocol of one of the preparations is shown.

1. Wet weight of tissue	583 gms.
2. Acetone-ether dried powder	98
3. Alcohol precipitated powder	0.698
4. Final product	0.170
5. Final yield	29%
6. Purification	170-fold

* Aided by a grant from the National Foundation for Infantile Paralysis, Inc. Submitted in partial fulfillment of requirements for degree of Doctor of Philosophy, Graduate School of Arts and Science, New York University.

TABLE I—PROPERTIES OF THE THEILER GD VII VIRUS INHIBITOR

Distribution			
Mouse Tissues	*Intestine of Other Species*	*Specificity*	*Carbohydrate Constituents***
Present:	Present:	Inhibits:	Present:
Adult Intestine	Guinea Pig	GD VII	Methyl Pentose
			Galactose
Variable:	Little or none:	Does not inhibit:	Mannose
Brain	Monkey	FA	Glucuronic Acid
	Rabbit	TO	Hexosamine
Little or none:	Hog	TO (Br)*	
Infant Intestine		Lansing	Absent:
Adult Heart			Glucose
Adult Lung			Ketohexose
Adult Kidney			
Adult Liver			
Adult Spleen			
Adult Muscle			

Stability	*Activity*
Stable to:	In vivo:
Autoclaving at neutral pH	0.03 ug reduced 1/T from 0.30 to 0.14
Prolonger storage at —25° C.	
Trypsin	In vitro:
Cathepsin	0.025 ug inhibted hemagglutination of 8 units
Ribonuclease	
Lysozyme	
Unstable to:	
100° C.—10 minutes in 1N HCl or NaOH	

* TO virus after seven passages through mouse brain.

** The analysis was kindly performed by Dr. Z. Dische of the College of Physicians and Surgeons of Columbia University.

An analysis of the final product showed that the major constituent was polysaccharide with about 10 per cent and 0.5 per cent nucleic acid also present.

Because of the presence of several molecular species, the question arose as to which one possessed the inhibitory activity. An attempt was made to answer this by chromatographic analysis. Using a paper strip impregnated with alumina and a phosphate buffer solvent, it was found that the carbohydrate and the inhibitory substance migrated at about the same rates. This may be considered as presumptive evidence that it is the polysaccharide which possesses the inhibitory activity.

The results of studies on the distribution and properties of the inhibitor are assembled in Table I.

It is interesting to note that on a dry weight basis infant mouse intestine shows considerably less inhibitory activity than adult intestine. It is also of interest that at approximately the same age level when TO virus first becomes detectable in the intestine, there is also a pronounced rise in the amount of inhibitory activity. These observations suggest a possible relationship between the receptor substance of the TO virus and the GD VII inhibitor. This hypothesis will be investigated.

A preliminary study of the mechanism of the inhibition reaction showed that virus can be inhibited only when it is inoculated simultaneously with, or shortly after, the inhibitor. This suggests that either, (a) virus and inhibitor combine to form a non-infectious and irreversible complex, or (b)

the inhibitor prevents the virus from reaching the receptor sites or some essential system of the host cells.

Relative Susceptibilities of the Central Nervous System and the Intestine of the Mouse to the TO Virus.—On the basis of Olitsky's observation[2] that very young mice are free of the TO virus, an attempt was made in 1947 to initiate a colony of Theiler-free mice. A number of 10-12 day old mice were decontaminated and transferred to an environment where contact with the TO virus was precluded. When the mice reached maturity they were tested and found to be free of TO virus. This colony of mice has been maintained in the Theiler-free state, under special precautions to prevent contamination, since the inception of this project.

The investigation of the relative susceptibilities of intestine and CNS was carried out as follows: Approximately four weeks old mice were divided into two groups. In one group the virus was titrated by the intracerebral inoculation of 0.03 ml. of appropriately diluted TO virus. The mice were observed for six weeks for symptoms of infection. In the second group the titration was carried out by feeding 0.3 ml. of the diluted virus preparation. One week after feeding, fecal samples were collected and tested for the presence of TO virus. The ID_{50} values were calculated on the basis of an inoculum of 0.03 ml. The values obtained for intestine and CNS were $10^{-4.4}$ and $10^{-3.3}$ respectively. This indicates that the intestine is more susceptible than the CNS. There is a possibility, however, that in the intestine there is also present a neurotropic mutant of the intestinal virus. If this should prove to be the case, then a reinterpretation of the above results would be required.

Summary

A substance has been isolated from adult mouse intestinal tissue which specifically inhibits the GD VII strain of Theiler's virus.

Presumptive evidence has been obtained that the inhibitor is a polysaccharide.

The amount of inhibitor that can be demonstrated in infant intestine is considerably less than that in the adult tissue.

Mouse intestine appears to be more susceptible than CNS to the TO virus when tested by parallel titrations in Theiler-free mice.

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*Chromatographic Analysis of Ragweed Pollen Extract**

ELY PERLMAN

Since it was discovered that crude extracts of ragweed and other pollens could be used for the treatment of hay fever, their use has become widespread. It is not surprising, therefore, that the problem of isolating the active component from crude extracts of pollens has engaged the efforts of numerous investigators.[1-3] The active constituent was variously thought to be a protein,[4, 5] a polysaccharide,[6-9] a polypeptide,[10] and a complex pigmented carbohydrate polypeptide.[11] More recent investigations have been accumulating evidence suggestive of the existence of two or more active constituents. Thus electrophoretic separation seems to yield two active components[13] and extensive tests on fractions obtained by salting-out methods provide similar evidence.[12, 13] In nearly all of the instances with the exception of reference 10, the fractions used were shown to be mixtures by electrophoretic analysis.[14]

In the present study, partition paper chromatography was applied to the problem of separating the numerous constituents present in crude extracts of giant ragweed pollen. The components were detected by a variety of tests and their activity was determined by elution from the paper and scratch-testing suitable, sensitive patients.

One gram of ether-defatted giant ragweed pollen was freshly extracted for each experiment with 5 ml. of water for two hours at 21°C. After centrifugation the supernatant in each experiment contained, quite uniformly, 2.2 mg N/ml. The extract was delivered from a fine capillary to form a thin band across one end of a narrow strip of Whatman's #1 filter paper. Eight applications were made to each strip after which the chromatogram was developed for eighteen hours by the ascending method, using as solvent a mixture of 1½ parts n-butanol, 1 part n-propanol, and 1 part distilled water. The strips were then dried in air and treated with a variety of reagents in order to detect as many constituents as possible. The results are shown in Fig. 1 where it is seen that at least two naturally occurring yellow pigments have separated (Y_1 and Y_2, Column D). Some seven purple bands are revealed by spraying with ninhydrin reagent[15] and are shown in Column C of Fig. 1. An intense scarlet band, whose position is shown in the same figure, results when the chromatogram is treated with α-naphtho-resorcinol (Column E).[16] Several reducing substances are present as shown by the dark bands obtained after treatment with ammoniacal silver nitrate (Column F).[17] An attempt was made to determine the presence of polysaccharides by means of Dreywood's anthrone reagent[18] which was used to test the material eluted from successive sections of the chromatogram (Column H). Some two additional bands were found when the extract was pretreated with hemin according to Franklin and Quastel.[19] The Sakaguchi test[20] showed the presence of arginine in component No, and examination of the chromatogram under ultraviolet light after treatment with various alkalis[21] suggests the presence of additional pigments.

Component No was eluted from the chromatogram, placed on a fresh strip of paper and developed with water-saturated 2-4-6 collidine. The results, following treatment with nihydrin reagent, suggest the presence of one major component in No which does not migrate, and small amounts of three additional components which separated from it.

The activity of each of these numerous components was determined by eluting them from the paper chromatogram and using the eluates to perform scratch tests on sensitive subjects. In these experiments the same type of ragweed pollen extract was used but was streaked across the entire width of an 18¼ by 22½ inch sheet of filter paper. Sev-

* From the Division of Bacteriology and the Medical Services, The Mount Sinai Hospital, New York, New York. This investigation was aided by grants from the Elsa and William Mencke Fund and from the Sarah Welt Memorial Fund.

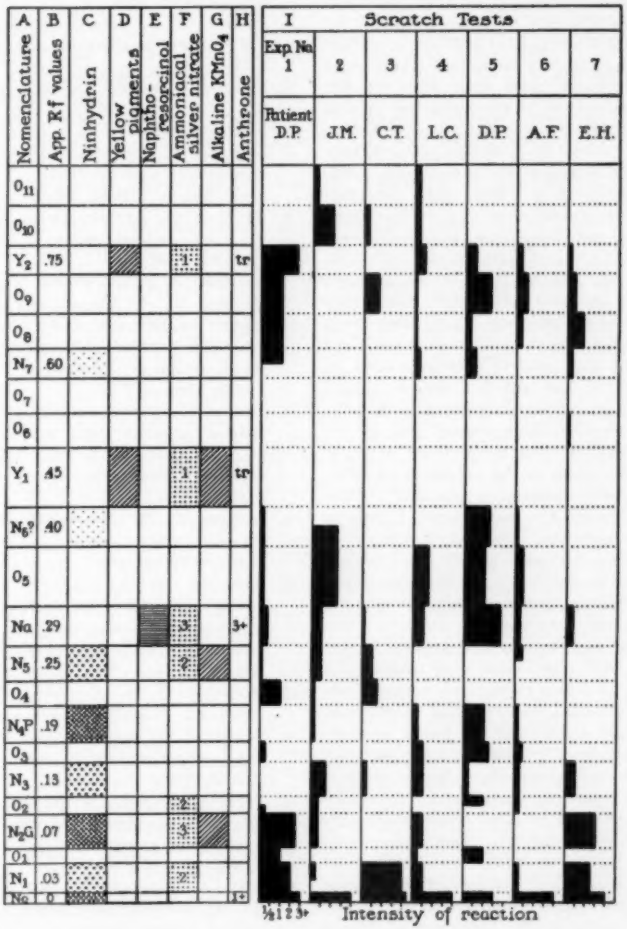

Fig. 1. Chromatographic analysis of ragweed pollen extract, showing the bands revealed by various chemical tests and the results of skin tests with the fractions eluted from each corresponding region of the chromatogram. See text.

eral narrow strips were cut from the chromatogram after development and were tested with several reagents. After the bands were identified and marked the strips were replaced onto the large sheet and the bands were interpolated onto the untouched portions of the chromatograms. These areas as well as the blank areas were cut out and each was extracted separately with a minimal amount of water. Each was then rubbed into a separate superficially scratched region of the skin of susceptible subjects. After a suitable time the reactions were graded from ½+ to 4+. Seven subjects and three normal controls were tested. The control subjects showed no reaction, and the reactions of the sensitive subjects are recorded in Fig. 1 where they are shown alongside the regions from which the eluates were obtained. It is immediately apparent that material associated with Y_1 was active, that material between regions N_6 and N_7 caused no reactions; that the eluate obtained from regions Na, O_2, N_4 was active and that No gave the strongest reactions. There is the suggestion of additional active material in region N_3P. The nitrogen content of these various eluates in no way correlated with their activity.

Experiments using paper pulp columns indicates the feasibility of using this method for obtaining larger amounts of material for further investigations.

Paper partition chromatography demonstrates the large number of components present in crude extracts of ragweed pollen. It affords a simple method for fractionating and for testing the purity of fractions obtained by this or other methods. The present application of paper chromatography provided a satisfactory separation of at least two or more active constituents from ragweed extract. These results have been generally confirmed by Drs. Arnold Dankner and S. C. Bukantz of Washington University School of Medicine, and by Dr. E. L. Becker of the University of Illinois College of Medicine.[22]

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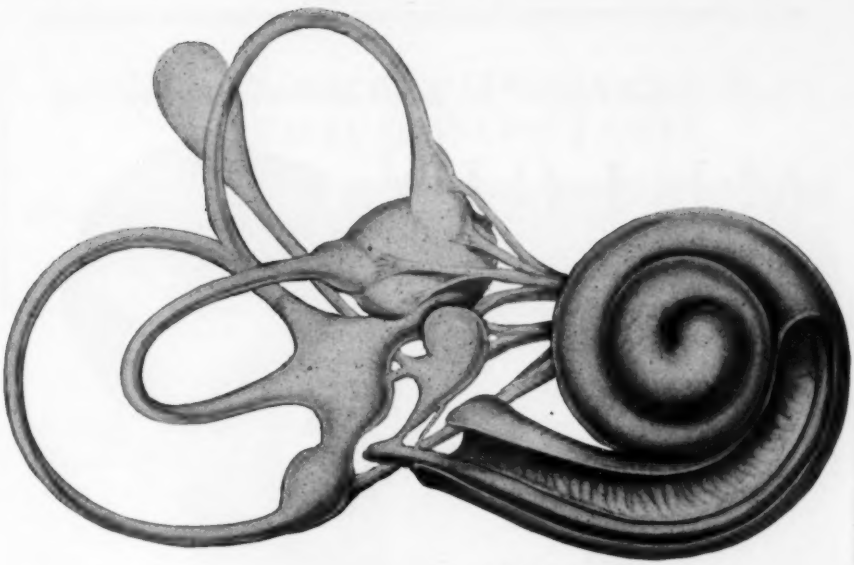

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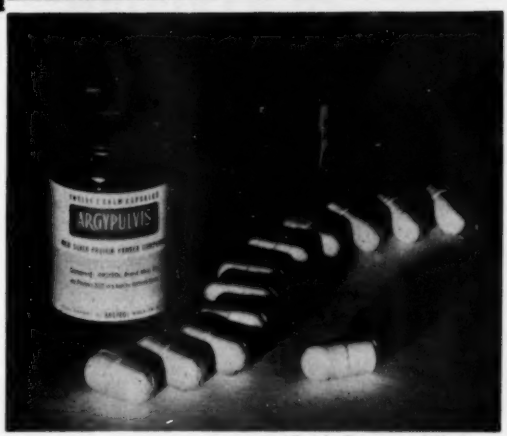

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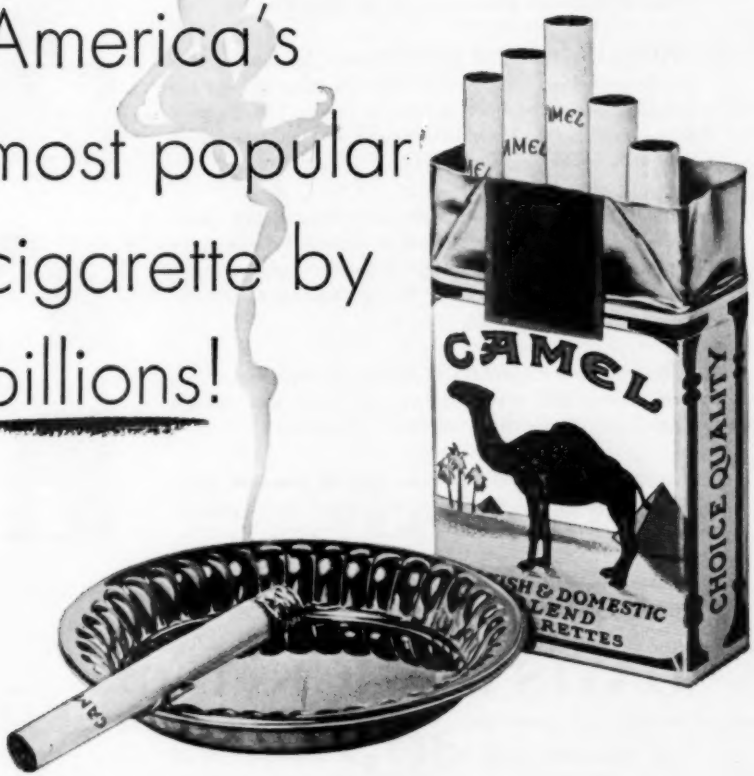

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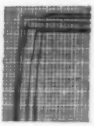
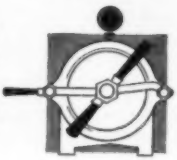
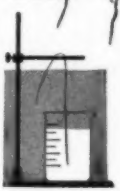


1. *Greater tensile strength:* One of the strongest silks ever created—smaller diameter sizes can be used everywhere to minimize trauma and foreign body reaction.



2. *Withstands repeated sterilization:* New Anacap Silk can be boiled or autoclaved *six separate times* without appreciable change in either strength or texture. In laboratory tests almost the full original strength is maintained even after 23½ hours of boiling.

3. *Easier to handle:* Firmer, not limp, Anacap Silk speeds operative technic. Braided by a new method that minimizes "splintering" and "whiskering" it passes readily through tissues. The ease of handling Anacap makes it a "new experience" in silk suturing.



4. *Absolute non-capillarity:* Having no wick-like action, new Anacap Silk is resistant to body fluids and will not spread an early localized infection if it occurs.

5. *Doubly economical:* Low in original purchase price, new Anacap Silk is also low in individual suture cost because of its long sterilization life.

In sizes 6-0 to 5 on spools of 25 and 100 yards; sterile in tubes with and without D & G Atraumatic® needles attached.

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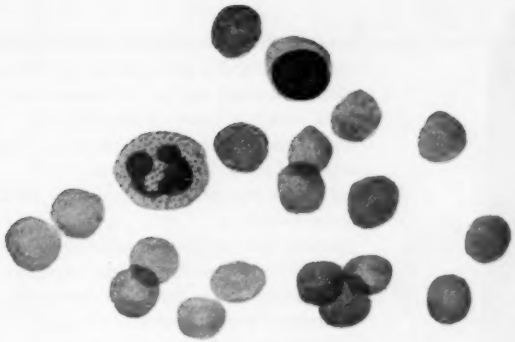
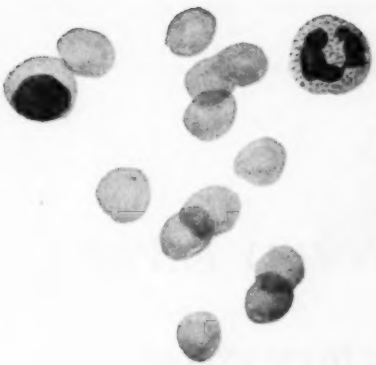


8 substances



Structural and functional integrity of the normal erythrocyte depends on a wide range of substances—8 of which are encompassed in each Cebetinic* tablet:

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Thiamine Hydrochloride	2.0 milligrams
Riboflavin	2.0 milligrams
Pyridoxine Hydrochloride	0.5 milligram
Nicotinamide	10.0 milligrams
Ascorbic Acid	25.0 milligrams

For anorexia, asthenia and anemia related to: nutritional deficits; post-infection and post-surgical states; chronic blood loss; gastro-intestinal disorders of absorption; periods of rapid growth in children; puberty and pregnancy—

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Dosage: AVERAGE ADULT — 3 tablets daily
CHILDREN—from 1 to 3 tablets daily, according to age
In bottles of 60 and 500 tablets

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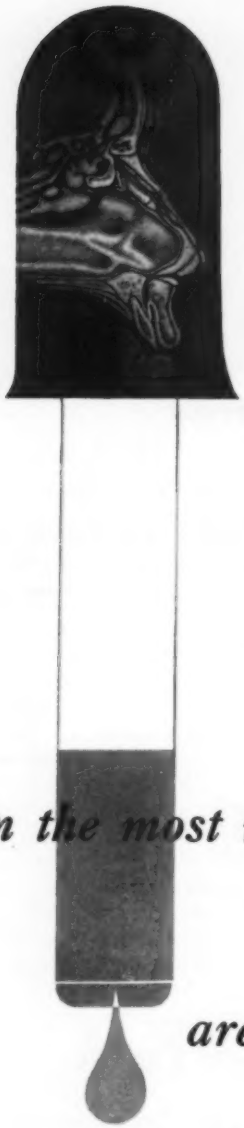

Antistine-Privine contains Antistine, to block the congestive action of histamine, and Privine, to shrink the nasal mucosa. Friedlaender and Friedlaender found that the decongestant action of Antistine-Privine on the allergic nasal mucosa "in many instances appears to be more intense and prolonged than from either solution alone!"

Systemic side reactions or rebound congestion are unlikely with Antistine-Privine because of the low concentrations of the active ingredients.

Antistine-Privine, aqueous solution of Antistine® (antazoline) hydrochloride, 0.5% and Privine® (naphazoline) hydrochloride, 0.025%, in bottles of 1 fl. oz. with dropper. 2/1000 M

1. Friedlaender, S. and Friedlaender, A. S.: Am. Pract. 2:643, 1948

Ciba Pharmaceutical Products, Inc., Summit, N.J.

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Local: ***Benzestrol*** **Vaginal Tablets:**
0.5 Mg. 100's.

AVERAGE DOSE: Menopause — 2 to 3 Mg. daily orally or ½ to 1cc parenterally every 5 days.

Professional Samples and Literature upon Request

NOTE:
Frequently, medication other than estrogens may be required during the menopause. Pleasant tasting Elixir Benzestrol is compatible with many substances.

*Reference: MacBryde, C. M., et. al., A New Synthetic Estrogen, J.A.M.A., 122: 261 (Sept. 18), 1943.

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Armbrust, C. A., Jr., and Levine, S. A.: Am.J.M.Sc. 220:127 (August) 1950	"About 60% of the cases showed improvement; i.e., used fewer nitroglycerin tablets, had fewer and milder attacks of pain and could walk greater distances."
Rosenman, R. H., et al.: J.A.M.A. 143:160 (May 13) 1950	"Of 14 patients with angina pectoris treated with ['Eskel']... a good response was obtained in 11, moderate improvement in 1 and no effect in 2."
Osher, H. L., et al.: New England J. Med. 244:315 (March 1) 1951	"Twenty-six of 32 patients were found to be benefited by ['Eskel'] therapy; ... no serious toxic reactions were encountered."

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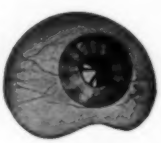

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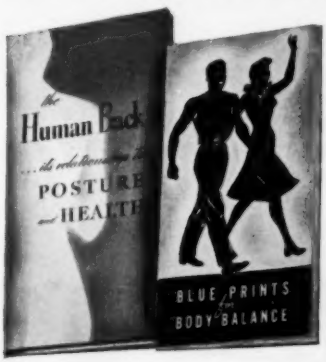

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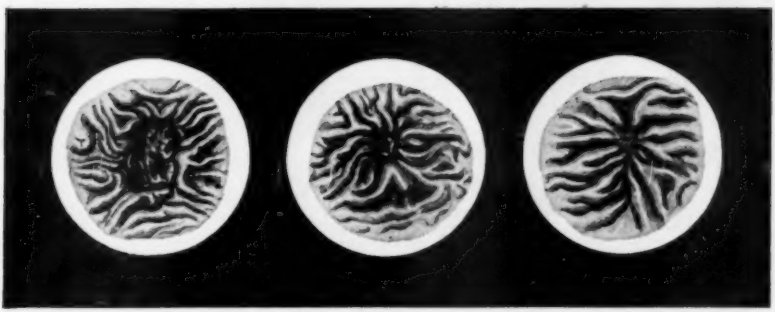

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*Brown et al.: *Ann. Allergy*, 8:88, 1950.

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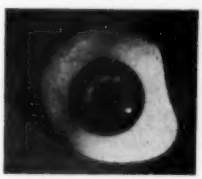

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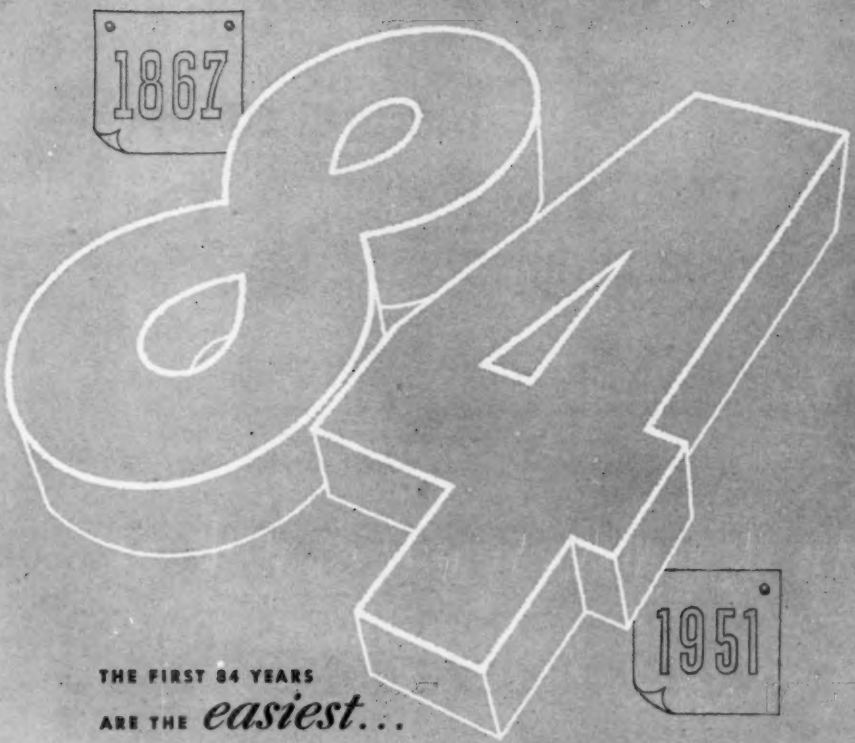

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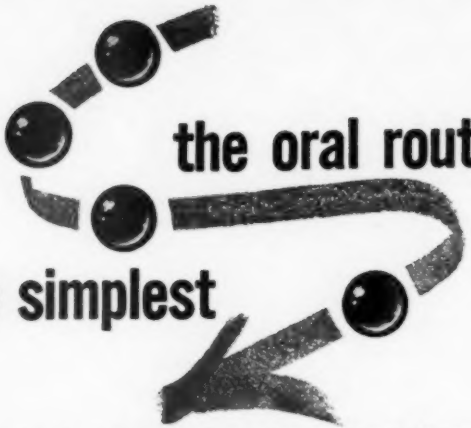

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